

## Efficacy and safety of subcutaneous trastuzumab and intravenous trastuzumab as part of adjuvant therapy for HER2-positive early breast cancer: final analysis of the randomised, two-cohort PrefHer study

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**Title:** Efficacy and safety of subcutaneous trastuzumab and intravenous trastuzumab as part of adjuvant therapy for HER2-positive early breast cancer: Final analysis of the randomised, two-cohort PrefHer study

**Author List:** X. Pivot <sup>a,\*</sup>, S. Verma <sup>b</sup>, L. Fallowfield <sup>c</sup>, V. Müller <sup>d</sup>, M. Lichinitser <sup>e</sup>, V. Jenkins <sup>c</sup>, A. Sánchez Muñoz <sup>f</sup>, Z. Machackova <sup>g</sup>, S. Osborne <sup>h</sup>, J. Gligorov <sup>i</sup>, on behalf of the PrefHer Study Group

<sup>a</sup> *University Hospital Jean Minjoz, INSERM 1098, Besançon, France;* <sup>b</sup> *Tom Baker Cancer Centre, Department of Oncology, University of Calgary, AB, Canada;*

<sup>c</sup> *Sussex Health Outcomes Research & Education in Cancer (SHORE-C), Brighton and Sussex Medical School, University of Sussex, Falmer, UK;* <sup>d</sup> *Department of Gynecology, University Medical Center Hamburg-Eppendorf, Hamburg, Germany;*

<sup>e</sup> *Department of Chemotherapy and Combined Therapy, N.N. Blokhin Cancer Research Center, Moscow, Russia;* <sup>f</sup> *Investigación Clínica y Traslacional en Cáncer/Instituto de Investigaciones Biomédicas de Málaga (IBIMA)/Hospitales Universitarios Regional y Virgen de la Victoria de Málaga, Málaga, Spain;* <sup>g</sup> *Global Product Development/Medical Affairs Oncology (PDMAO), F. Hoffmann-La Roche Ltd, Basel, Switzerland;* <sup>h</sup> *PDMA Operations (Biometrics), F. Hoffmann-La Roche Ltd, Basel, Switzerland;* <sup>i</sup> *Medical Oncology Department; APHP-Tenon; IUC-UPMC; Sorbonne University, Paris, France.*

**\* Corresponding author**

Prof. Xavier Pivot

Department of Medical Oncology

University Hospital Jean Minjoz

INSERM 1098

25030 Besançon

France

Telephone: +33-381-669-212;

Fax: +33-381-668-858;

E-mail: xavier.pivot@univ-fcomte.fr

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## **Abstract**

**Aim:** To assess efficacy (event-free survival, EFS) and safety in patients followed up for 3 years in the PrefHer study (NCT01401166).

**Patients and methods:** Post-surgery and -chemotherapy in the (neo)adjuvant setting, patients with HER2-positive early breast cancer were randomised to receive four cycles of the subcutaneous form of trastuzumab (Herceptin® SC [H SC] via single-use injection device [Cohort 1] or delivery via a hand-held syringe from an SC Vial [Cohort 2]; 600 mg fixed dose) followed by four of the intravenous form of trastuzumab (Herceptin® [H IV]; 8 mg/kg loading, 6 mg/kg maintenance doses) in the adjuvant setting, or vice versa, every 3 weeks. Patients could have received H before randomisation. H was then continued to complete a total of 18 cycles, including any cycles received before randomisation.

**Results:** A total of 488 patients were randomised across both cohorts. After median follow-up of 36.1 months, 3-year EFS across both groups in the evaluable intention-to-treat population (467 patients) was 90.6% overall, 89.9% in Cohort 1, and 91.1% in Cohort 2. No new safety signals were identified during long-term follow-up, with only one cardiac serious adverse event in the safety population (483 patients).

**Conclusions:** Three-year EFS data following H SC and H IV treatment are consistent with those reported by previous trials for H in the adjuvant setting. The overall safety profile during adjuvant treatment was as expected.

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## 1. Introduction

Trastuzumab (Herceptin® [H], F. Hoffmann-La Roche Ltd, Basel, Switzerland)-containing regimens are now standard of care for patients with HER2-positive breast cancer. A 600 mg fixed-dose manual injection of the subcutaneous form of H (Herceptin® SC [H SC], F. Hoffmann-La Roche Ltd), given via hand-held syringe from an H SC Vial, was approved following demonstrated non-inferiority compared with the intravenous form of H (H IV) based on pathological complete response and serum trough concentration in the HannaH study.[1] To date, over two million patients with breast cancer have been treated with H; approximately 80,000 of which were treated with H SC (F. Hoffmann-La Roche Ltd, data on file). The international, open-label, randomised, crossover PrefHer study (NCT01401166) investigated patient preference for H SC or H IV during the adjuvant treatment of HER2-positive early breast cancer. The study revealed overwhelming patient preferences for H SC (89%), regardless of the method of H SC delivery: single-use injection device (SID) or delivery via a hand-held syringe from an SC Vial, with 'time saving' and 'less pain/discomfort/side effects' the most common reasons given by the patients themselves during interviews.[2–4] There was a high preference for H SC irrespective of whether or not patients received H IV prior to study enrolment.[2,3] In addition, patients' preferences for H SC for metastatic breast cancer have been demonstrated in the Metaspher study.[5] A time-and-motion study within the PrefHer study demonstrated a mean time saving of 55–57 min of patient chair time and 13–17 min of active healthcare professional time per session with H SC compared with H IV,[6] and several

countries have reported estimated increased hospital capacity and/or cost-savings with H SC.[7–17] These data support a transition to SC delivery. We present efficacy and safety data after 3 years' follow-up in the PrefHer study.

## **2. Patients and Methods**

### *2.1 Patients*

Eligibility criteria have been described previously [2] and are available in the appendix.

### *2.2 Study design*

Following surgery and completion of chemotherapy in the (neo)adjuvant setting, patients received four cycles of H SC (600 mg fixed dose injected over approximately 5 min into the thigh) every 3 weeks followed by four cycles of H IV (6 mg/kg) in the adjuvant setting, or vice versa (Fig. 1).[2] An H IV loading dose of 8 mg/kg was required only if the first cycle of study treatment was the initial IV dose of H (i.e., H IV/H SC); otherwise, the dose was 6 mg/kg every 3 weeks. Following these eight cycles (the crossover period), patients continued H SC or H IV therapy to complete 18 standard cycles (1 year) (H continuation period).

During crossover, patients in Cohort 1 received H SC via SID and patients in Cohort 2 received H SC via hand-held syringe from an H SC Vial.

Patients could have been either H-naïve (*de novo*) or could have already started H for early breast cancer prior to study entry (non-*de novo*), but

needed to receive at least eight more cycles to complete 1 year (18 cycles) of H in the adjuvant setting.

Following crossover, i.e. the H continuation period, it was planned for patients in Cohort 1 to receive H IV (unless choosing to self-administer H SC via SID), and for patients in Cohort 2 to receive H SC via hand-held syringe from an H SC Vial.

Following completion of H, patients were followed up for 3 years from randomisation (follow-up period).

The primary endpoint was patient preference (reported previously).[2,3]

Secondary endpoints included event-free survival, safety and tolerability.

PrefHer was conducted in accordance with Good Clinical Practice guidelines and the Declaration of Helsinki. All participating patients provided written informed consent. Approval for the protocol was obtained from appropriate local and national independent ethics committees.

### *2.3 Statistical considerations*

EFS was assessed using the Kaplan–Meier approach and is presented for the overall evaluable intention-to-treat (ITT) populations (patients who completed the primary preference question and  $\geq 1$  administration of both H SC and H IV) for each cohort, and overall. EFS was defined as the time from randomisation to local, regional or distant disease recurrence, contralateral breast cancer or death from any cause.

Adverse events (AEs) and serious AEs (SAEs) were reported according to National Cancer Institute – Common Terminology Criteria for Adverse Events v4.0 and New York Heart Association criteria. Safety data are presented for

the overall safety population (patients who received at least one dose of study treatment) and by treatment period.

### **3. Results**

#### *3.1 Patients*

The trial profile is shown in Supplementary Fig. 1. Four hundred and eighty-eight patients were randomised, 483 were included in the safety population, and 467 were included in the evaluable ITT population.[3] The *de novo* group comprised 98/483 patients (20.3%) and the non-*de novo* group 385/483 patients (79.7%). Four hundred and nine patients completed follow-up according to protocol. Baseline characteristics and treatment history are shown in Table 1 for the evaluable ITT population and Table 2 for the safety population.

#### *3.2 EFS*

After a median follow-up of 36.1 months (range 0–45.9 months), 3-year EFS across both randomisation groups in the overall evaluable ITT population was 90.6% overall (95% confidence interval [CI] 87.4–92.9%) (Fig. 2A), 89.9% in Cohort 1 (95% CI 84.9–93.3%) (Fig. 2B), and 91.1% in Cohort 2 (95% CI 86.6–94.2%) (Fig. 2C). Overall, 46/467 patients (9.9%) had an EFS event by the end of follow-up: 16/467 (3.4%) had a local occurrence, 8/467 (1.7%) a regional occurrence, 30/467 (6.4%) a distant recurrence and 3/467 (0.6%) had contralateral breast cancer (patients could have been counted in more than one event-type but only once overall).



### 3.3 Safety

Taking into account the H cycles received prior to randomisation, 425/483 (88.0%) patients in the safety population received all 18 H cycles, with a median of 13 on-study. The majority of patients in the *de novo* group (89/98, 90.8%) completed all 18 H cycles and, taking into account cycles received before randomisation, the majority of non-*de novo* patients (336/385, 87.3%) also completed all 18 H cycles. Forty-three patients in Cohort 1 received H SC by SID during the continuation period, with the remainder receiving H IV. In Cohort 2, ten patients chose to receive H IV during the continuation period, with the remainder receiving H SC via hand-held syringe from an H SC Vial. Among the 58/483 patients (12.0%) in the safety population who discontinued treatment before the end of the planned 18 cycles, the most common reasons for treatment discontinuation were adverse events (22 patients, 4.6%) and disease recurrence (14 patients, 2.9%). No deaths occurred on-treatment. A total of 409 patients completed follow-up, including 30 of the patients who had previously discontinued treatment.

The most common AEs of any grade were arthralgia (13.7%), asthenia (13.7%) and headache (10.4%) (Table 1). No other AEs occurred in  $\geq 10\%$  of patients (Table 3). Differences in AE rates between H SC and H IV periods during crossover (Table 4) were driven by injection site reactions, and rates were similar between H SC and H IV periods when injection site reactions were excluded (275/479 [57.4%] and 258/478 [54.0%], respectively).

Most AEs were grades 1 or 2, with grade 3 events in 45 patients (9.3%) (Table 4). No grade 4 or 5 AEs were reported. AEs considered by the investigator to be related to H treatment were reported in 213 patients

(44.1%), and at grade 3 severity in 14 patients (2.9%). Left ventricular dysfunction and dyspnoea (two patients each) were the only H-related grade 3 AEs that occurred in more than one patient.

SAEs were reported in 19/483 patients (3.9%) (Table 4). Only one (left ventricular dysfunction in one Cohort 2 patient during the H SC continuation period) was considered by the investigator to be related to H treatment. This resulted in temporary discontinuation of study drug; the patient recovered completely. All SAEs had resolved by clinical cut-off.

AEs resulted in treatment discontinuation in 21/483 patients (4.3%), 7/244 (2.9%) in Cohort 1 and 14/239 (5.9%) in Cohort 2. Left ventricular dysfunction (one patient in Cohort 1 and six in Cohort 2), congestive cardiac failure (one patient in Cohort 1 and two in Cohort 2) and injection site pain (two patients in Cohort 2) were the only AEs that led to discontinuation in more than one patient. There were eight deaths during the study, two in Cohort 1 and six in Cohort 2. All were attributed to disease recurrence.

### *3.4 Cardiac AEs*

A total of 49 cardiac AEs were reported in 40/483 patients (8.3%), with left ventricular dysfunction (11 patients, 2.3%), palpitations (seven patients, 1.4%), ejection fraction decreased (seven patients, 1.4%), congestive cardiac failure (five patients, 1.0%), bradycardia (three patients, 0.6%) and extrasystoles (two patients, 0.4%) being the only cardiac AEs occurring in more than one patient (Table 5). Most cardiac events were grades 1 and 2, with only one cardiac SAE (left ventricular dysfunction; described above). Only four patients had grade 3 cardiac events; three experienced left ventricular

dysfunction (one in Cohort 1, two in Cohort 2) and one patient in Cohort 2 experienced congestive heart failure. No patients experienced serious congestive heart failure.

#### **4. Discussion**

The PrefHer study demonstrated an overwhelming patient preference (89%) for treatment with H SC over H IV during the adjuvant treatment of HER2-positive early breast cancer, regardless of the method of H SC delivery (SID or delivery via a hand-held syringe from an SC Vial,[2,3]) with clear and meaningful benefits in time saving for both patients and healthcare professionals in addition to patient-reported advantages of convenience and less pain/discomfort/side effects.[2–4] SC delivery of a 600 mg fixed dose was shown to result in non-inferior trough H serum concentrations and pathological complete response compared with body-weight-based IV dosing in the HannaH study.[1] EFS was also similar between H SC and H IV after 2 years of treatment-free follow-up.[18] Recently, studies including HannaH showed that pathological complete response was associated with EFS.[18–20] In the current report we describe 3-year efficacy and safety of H SC in the PrefHer study.

Overall, the 3-year EFS rates following H SC and H IV treatment observed in both cohorts were consistent with efficacy observed in previous clinical trials of adjuvant H therapy for patients with HER2-positive early breast cancer.[21–24]

Previous safety analyses of PrefHer, which were limited to the crossover period, have indicated that H SC was well tolerated, with no new safety

signals identified,[2,3] and that safety was not affected by switching from H IV to H SC or vice versa.[25] The 3-year results of PrefHer presented here confirm these findings. No additional safety signals were identified and safety was as expected during the crossover periods and H continuation periods in both cohorts. Long-term analyses of cardiac events in phase III trials of H show that late congestive heart failure is uncommon, with most events occurring during treatment, and that the majority of cardiac events are reversible.[26–33] Our data are consistent with these findings, with few grade 3 cardiac AEs and only one cardiac SAE in 483 patients. There were no associations between cardiac safety and method of delivery (SID or hand-held syringe from an H SC Vial) or phase of treatment during the trial.

A limitation of the current study is that, because patients received both H IV and H SC and may have switched between the two on one or more occasions, analysis of subgroups, e.g. by body weight, would be difficult to interpret, and therefore these have not been performed. Previous studies, however, have shown that the efficacy and safety of H SC is comparable in patients of low and high body weight.[1,18,34]

H remains a key component of treatment for HER2-positive breast cancer, both in the (neo)adjuvant and metastatic settings. Recent long-term data from the NeoSphere and APHINITY studies were of particular interest, as they suggested a progression-free and (invasive) disease-free survival benefit of combining anti-HER2 therapies (pertuzumab and H) with chemotherapy in the neoadjuvant and adjuvant settings, respectively.[20,35] The survival benefit of H plus pertuzumab and docetaxel is also proven in the metastatic setting.[36,37] Combining pertuzumab with H SC may provide further benefits

and convenience for patients in the future and the safety profile of this combination in metastatic breast cancer has been reported in the phase IIb SAPPHIRE study [38] and the phase III MetaPHER study.[39] However, as observed in PrefHer [2, 3], a small proportion of patients prefer H IV and can ask for it. In conclusion, 3-year EFS results following H SC and H IV treatment confirm efficacy findings from previous trials of H in the adjuvant setting. H SC was well tolerated and no new safety signals were identified compared with the known profiles of H IV or H SC from previous reports in HER2-positive early breast cancer.

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## Figures and tables

**Table 1 – Patient characteristics (evaluable ITT population).**

<sup>a</sup> Denominator = 116. <sup>b</sup> Denominator = 117. <sup>c</sup> Denominator = 116.

<sup>d</sup> Denominator = 110. <sup>e</sup> Denominator = 459.

**Abbreviations:** H, trastuzumab (Herceptin®); ECOG PS, Eastern Cooperative Oncology Group performance status; IV, intravenous; SC, subcutaneous.

|   | <b>Cohort 1</b>                   |                                   | <b>Cohort 2</b>                   |                                   |                                   |
|---|-----------------------------------|-----------------------------------|-----------------------------------|-----------------------------------|-----------------------------------|
|   | <b>H SC→<br/>H IV<br/>n = 117</b> | <b>H IV→<br/>H SC<br/>n = 119</b> | <b>H SC→<br/>H IV<br/>n = 118</b> | <b>H IV→<br/>H SC<br/>n = 113</b> | <b>Overall<br/>N = 467</b>        |
| Median age, years (range)               | 54.0 (32–76)                      | 51.0 (28–75)                      | 50.0 (29–78)                      | 53.0 (27–76)                      | 52.0 (27–78)                      |
| Median weight, kg (range)               | 68.6<br>(35.0–12.0) <sup>a</sup>  | 66.0<br>(45.0–131.8) <sup>b</sup> | 67.5<br>(49.0–103.8) <sup>c</sup> | 65.5<br>(41.0–117.0) <sup>d</sup> | 67.0<br>(35.0–131.8) <sup>e</sup> |
| Oestrogen receptor status, n (%)        |                                   |                                   |                                   |                                   |                                   |
| Negative                                | 39 (33.3)                         | 40 (33.6)                         | 40 (33.9)                         | 41 (36.3)                         | 160 (34.3)                        |
| Positive                                | 77 (65.8)                         | 79 (66.4)                         | 74 (62.7)                         | 71 (62.8)                         | 301 (64.5)                        |
| Unknown                                 | 1 (0.9)                           | 0                                 | 4 (3.4)                           | 1 (0.9)                           | 6 (1.3)                           |
| ECOG PS at screening, n (%)             |                                   |                                   |                                   |                                   |                                   |
| 0                                       | 95 (81.2)                         | 96 (80.7)                         | 99 (83.9)                         | 91 (80.5)                         | 381 (81.6)                        |
| 1                                       | 22 (18.8)                         | 23 (19.3)                         | 19 (16.1)                         | 21 (18.6)                         | 85 (18.2)                         |
| Not done                                | 0                                 | 0                                 | 0                                 | 1 (0.9)                           | 1 (0.2)                           |
| TNM classification at diagnosis, n (%)  |                                   |                                   |                                   |                                   |                                   |
| T0                                      | 1 (0.9)                           | 3 (2.5)                           | 0                                 | 1 (0.9)                           | 5 (1.1)                           |
| T1                                      | 62 (53.0)                         | 40 (33.6)                         | 47 (39.8)                         | 51 (45.1)                         | 200 (42.8)                        |
| T2                                      | 38 (32.5)                         | 57 (47.9)                         | 61 (51.7)                         | 43 (38.1)                         | 199 (42.6)                        |
| T3                                      | 8 (6.8)                           | 11 (9.2)                          | 5 (4.2)                           | 12 (10.6)                         | 36 (7.7)                          |
| T4                                      | 6 (5.1)                           | 8 (6.7)                           | 3 (2.5)                           | 6 (5.3)                           | 23 (4.9)                          |
| Not assessable/<br>unknown              | 2 (1.7)                           | 0                                 | 2 (1.7)                           | 0                                 | 4 (0.9)                           |
| Lymph node-positive at diagnosis, n (%) | 48 (41.0)                         | 66 (55.5)                         | 61 (51.7)                         | 53 (46.9)                         | 228 (48.8)                        |
| H before enrolment, n (%)               |                                   |                                   |                                   |                                   |                                   |
| <i>De novo</i>                          | 27 (23.1)                         | 27 (22.7)                         | 20 (16.9)                         | 20 (17.7)                         | 94 (20.1)                         |
| <i>Non-de novo</i>                      | 90 (76.9)                         | 92 (77.3)                         | 98 (83.1)                         | 93 (82.3)                         | 373 (79.9)                        |
| Previous treatment, n (%)               |                                   |                                   |                                   |                                   |                                   |
| Chemotherapy                            | 117 (100)                         | 119 (100)                         | 117 (99.2)                        | 113 (100)                         | 466 (99.8)                        |
| Radiotherapy                            | 75 (64.1)                         | 74 (62.2)                         | 71 (60.2)                         | 68 (60.2)                         | 288 (61.7)                        |
| Hormonal therapy                        | 50 (42.7)                         | 52 (43.7)                         | 48 (40.7)                         | 44 (38.9)                         | 194 (41.5)                        |
| Lapatinib                               | 0                                 | 1 (0.8)                           | 0                                 | 1 (0.9)                           | 2 (0.4)                           |

**Table 2 – Patient characteristics (safety population).**

<sup>a</sup> Denominator = 121. <sup>b</sup> Denominator = 120. <sup>c</sup> Denominator = 119.

<sup>d</sup> Denominator = 115. <sup>e</sup> Denominator = 475.

**Abbreviations:** H, trastuzumab (Herceptin®); ECOG PS, Eastern Cooperative Oncology Group performance status; IV, intravenous; SC, subcutaneous.

|  | Cohort 1                        |                                 | Cohort 2                        |                                 |                                |
|--|---------------------------------|---------------------------------|---------------------------------|---------------------------------|--------------------------------|
|  | H SC→<br>H IV<br><i>n</i> = 122 | H IV→<br>H SC<br><i>n</i> = 122 | H SC→<br>H IV<br><i>n</i> = 121 | H IV→<br>H SC<br><i>n</i> = 118 | Overall<br><i>N</i> = 483      |
| Median age, years (range)                      | 55.0 (32–83)                    | 51.0 (28–75)                    | 50.0 (29–78)                    | 53.0 (27–76)                    | 53.0 (27–83)                   |
| Median weight, kg (range)                      | 69.0 (35.0–120.0) <sup>a</sup>  | 65.7 (45.0–131.8) <sup>b</sup>  | 67.0 (49.0–103.8) <sup>c</sup>  | 66.0 (41.0–117.0) <sup>d</sup>  | 67.0 (35.0–131.8) <sup>e</sup> |
| Oestrogen receptor status, <i>n</i> (%)        |                                 |                                 |                                 |                                 |                                |
| Negative                                       | 44 (36.1)                       | 40 (32.8)                       | 40 (33.1)                       | 44 (37.3)                       | 168 (34.8)                     |
| Positive                                       | 77 (63.1)                       | 82 (67.2)                       | 77 (63.6)                       | 73 (61.9)                       | 309 (64.0)                     |
| Unknown  | 1 (0.8)                         | 0                               | 4 (3.3)                         | 1 (0.8)                         | 6 (1.2)                        |
| ECOG PS at screening, <i>n</i> (%)             |                                 |                                 |                                 |                                 |                                |
| 0  | 97 (79.5)                       | 98 (80.3)                       | 102 (84.3)                      | 93 (78.8)                       | 390 (80.7)                     |
| 1  | 25 (20.5)                       | 24 (19.7)                       | 19 (15.7)                       | 14 (20.3)                       | 92 (19.0)                      |
| Not done                                       | 0                               | 0                               | 0                               | 1 (0.8)                         | 1 (0.2)                        |
| TNM classification at diagnosis, <i>n</i> (%)  |                                 |                                 |                                 |                                 |                                |
| T0   | 1 (0.8)                         | 3 (2.5)                         | 0                               | 1 (0.8)                         | 5 (1.0)                        |
| T1   | 64 (52.5)                       | 41 (33.6)                       | 48 (39.7)                       | 51 (43.2)                       | 204 (42.2)                     |
| T2   | 40 (32.8)                       | 59 (48.4)                       | 63 (52.1)                       | 46 (39.0)                       | 208 (43.1)                     |
| T3   | 8 (6.6)                         | 11 (9.0)                        | 5 (4.1)                         | 13 (11.0)                       | 37 (7.7)                       |
| T4   | 7 (5.7)                         | 8 (6.6)                         | 3 (2.5)                         | 7 (5.9)                         | 25 (5.2)                       |
| Not assessable/unknown                         | 2 (1.6)                         | 0                               | 2 (1.7)                         | 0                               | 4 (0.8)                        |
| Lymph node-positive at diagnosis, <i>n</i> (%) | 51 (41.8)                       | 67 (54.9)                       | 63 (52.1)                       | 57 (48.3)                       | 238 (49.3)                     |
| H before enrolment, <i>n</i> (%)               |                                 |                                 |                                 |                                 |                                |
| <i>De novo</i>                                 | 28 (23.0)                       | 29 (23.8)                       | 21 (17.4)                       | 20 (16.9)                       | 98 (20.3)                      |
| Non- <i>de novo</i>                            | 94 (77.0)                       | 93 (76.2)                       | 100 (82.6)                      | 98 (83.1)                       | 385 (79.7)                     |
| Previous treatment, <i>n</i> (%)               |                                 |                                 |                                 |                                 |                                |
| Chemotherapy                                   | 122 (100)                       | 122 (100)                       | 120 (99.2)                      | 118 (100)                       | 482 (99.8)                     |
| Radiotherapy                                   | 76 (62.3)                       | 76 (62.3)                       | 73 (60.3)                       | 70 (59.3)                       | 295 (61.1)                     |
| Hormonal therapy                               | 50 (41.0)                       | 55 (45.1)                       | 50 (41.3)                       | 45 (38.1)                       | 200 (41.4)                     |
| Lapatinib                                      | 0                               | 1 (0.8)                         | 1 (0.8)                         | 1 (0.8)                         | 3 (0.6)                        |

**Table 3 – Adverse events in ≥5% patients in any period (safety population).** <sup>a</sup> Could be counted once per grade but ≥ once overall.

**Abbreviations:** AE, adverse event; H, trastuzumab (Herceptin®); IV, intravenous; SC, subcutaneous; SID, single-use injection device.

|                                     | Crossover                     |                               |  | Continuation                                   |                             | Overall        |
|-------------------------------------|-------------------------------|-------------------------------|--|--|-----------------------------|----------------|
| Patients, <i>n</i> (%) <sup>a</sup> | H SC period<br><i>n</i> = 479 | H IV period<br><i>n</i> = 478 | <i>P</i> value<br>(H SC period<br>vs. H IV period) | H IV or<br>H SC<br>(syringe)<br><i>n</i> = 440 | H SC (SID)<br><i>n</i> = 43 | <i>N</i> = 483 |
| Any AE                              | 300 (62.6)                    | 258 (54.0)                    | 0.01   | 223 (50.7)                                     | 12 (27.9)                   | 388 (80.3)     |
| Arthralgia                          | 25 (5.2)                      | 27 (5.6)                      | 0.78   | 22 (5.0)                                       | 1 (2.3)                     | 66 (13.7)      |
| Asthenia                            | 30 (6.3)                      | 25 (5.2)                      | 0.58   | 20 (4.5)                                       | 0                           | 66 (13.7)      |
| Headache                            | 20 (4.2)                      | 17 (3.6)                      | 0.74   | 21 (4.8)                                       | 0                           | 50 (10.4)      |
| Hot flush                           | 22 (4.6)                      | 17 (3.6)                      | 0.51   | 8 (1.8)  | 1 (2.3)                     | 45 (9.3)       |
| Fatigue                             | 19 (4.0)                      | 18 (3.8)                      | 1.00   | 13 (3.0)                                       | 0                           | 44 (9.1)       |
| Nausea                              | 25 (5.2)                      | 14 (2.9)                      | 0.10   | 9 (2.0)  | 1 (2.3)                     | 39 (8.1)       |
| Injection site pain                 | 32 (6.7)                      | 0                             | <0.01  | 6 (1.4)  | 2 (4.7)                     | 37 (7.7)       |
| Diarrhoea                           | 16 (3.3)                      | 12 (2.5)                      | 0.57   | 12 (2.7)                                       | 0                           | 35 (7.2)       |
| Pain in extremity                   | 19 (4.0)                      | 7 (1.5)                       | 0.03   | 8 (1.8)  | 0                           | 31 (6.4)       |
| Injection site erythema             | 28 (5.8)                      | 0                             | <0.01  | 4 (0.9)  | 0                           | 30 (6.2)       |
| Injection site reaction             | 29 (6.1)                      | 0                             | <0.01  | 2 (0.5)  | 0                           | 29 (6.0)       |
| Nasopharyngitis                     | 11 (2.3)                      | 10 (2.1)                      | 1.00   | 12 (2.7)                                       | 1 (2.3)                     | 29 (6.0)       |
| Erythema                            | 17 (3.5)                      | 6 (1.3)                       | 0.03   | 7 (1.6)  | 1 (2.3)                     | 26 (5.4)       |

**Table 4 – Adverse event profile (safety population).** <sup>a</sup> Could be counted

once per grade but  $\geq$  once overall.

**Abbreviations:** AE, adverse event; H, trastuzumab (Herceptin®); IV, intravenous; SC, subcutaneous; SAE, serious adverse event; SID, single-use injection device.

|  | Crossover                        |                               | P value<br>(H SC<br>period<br>vs. H IV<br>period) | Continuation                                   |                             | Overall        |
|--|----------------------------------|-------------------------------|---|--|-----------------------------|----------------|
| Patients with<br>$\geq 1$ AE, <i>n</i> (%) <sup>a</sup>                  | H SC<br>period<br><i>n</i> = 479 | H IV period<br><i>n</i> = 478 |   | H IV or<br>H SC<br>(syringe)<br><i>n</i> = 440 | H SC (SID)<br><i>n</i> = 43 | <i>N</i> = 483 |
| Median H<br>cycles, <i>n</i>   | 4.0                              | 4.0                           | –   | 5.0  | 2.0                         | 13.0           |
| Any AE   | 300 (62.6)                       | 258 (54.0)                    | 0.01  | 223 (50.7)                                     | 12 (27.9)                   | 388 (80.3)     |
| Grade 1  | 262 (54.7)                       | 206 (43.1)                    | <0.01   | 175 (39.8)                                     | 10 (23.3)                   | 360 (74.5)     |
| Grade 2  | 119 (24.8)                       | 110 (23.0)                    | 0.54  | 85 (19.3)                                      | 5 (11.6)                    | 214 (44.3)     |
| Grade 3  | 17 (3.5)                         | 16 (3.3)                      | 1.00  | 16 (3.6)                                       | 1 (2.3)                     | 45 (9.3)       |
| Grade 4  | 0                                | 0                             | –   | 0  | 0                           | 0              |
| Grade 5  | 0                                | 0                             | –   | 0  | 0                           | 0              |
| AE with<br>suspected<br>causal<br>relationship to<br>study<br>medication | 163 (34.0)                       | 53 (11.1)                     | <0.01   | 60 (13.6)                                      | 4 (9.3)                     | 207 (42.9)     |
| Discontinuation<br>for AE  | 5 (1.0)                          | 6 (1.3)                       | 0.77  | 10 (2.3)                                       | 0                           | 21 (4.3)       |
| Any SAE  | 4 (0.8)                          | 4 (0.8)                       | 1.00  | 11 (2.5)                                       | 1 (2.3)                     | 19 (3.9)       |
| Treatment-<br>related SAE  | 0                                | 0                             | –   | 1 (0.2)  | 0                           | 1 (0.2)        |



**Table 5 – Cardiac adverse events (safety population).** <sup>a</sup> Could be counted once per grade but  $\geq$  once overall. <sup>b</sup> Cardiac disorders not listed: bradycardia (three patients), extrasystoles (two patients), angina pectoris, cardiomyopathy, diastolic dysfunction, heart valve incompetence, left ventricular hypertrophy, mitral valve incompetence, sinus bradycardia, tachycardia (one patient each). <sup>c</sup> Ejection fraction decreased (seven patients), ejection fraction abnormal, electrocardiogram change (one patient each).

**Abbreviations:** AE, adverse event; H, trastuzumab (Herceptin®); IV, intravenous; SC, subcutaneous; SID, single-use injection device.

|  | Crossover                     |                               | Continuation                                   |                             | Overall        |
|--|-------------------------------|-------------------------------|--|-----------------------------|----------------|
| Patients with $\geq 1$ AE, <i>n</i> (%) <sup>a</sup> | H SC period<br><i>n</i> = 479 | H IV period<br><i>n</i> = 478 | H IV or<br>H SC<br>(syringe)<br><i>n</i> = 440 | H SC (SID)<br><i>n</i> = 43 | <i>n</i> = 483 |
| Any cardiac AE                                       | 12 (2.5)                      | 15 (3.1)                      | 17 (3.9)                                       | 0                           | 40 (8.3)       |
| Grade 1  | 9 (1.9)                       | 11 (2.3)                      | 11 (2.5)                                       | 0                           | 28 (5.8)       |
| Grade 2  | 2 (0.4)                       | 3 (0.6)                       | 6 (1.4)  | 0                           | 10 (2.1)       |
| Grade 3  | 1 (0.2)                       | 2 (0.4)                       | 1 (0.2)  | 0                           | 4 (0.8)        |
| Cardiac disorders (any grade) <sup>b</sup>           | 8 (1.7)                       | 14 (2.9)                      | 14 (3.2)                                       | 0                           | 33 (6.8)       |
| Left ventricular dysfunction                         | 2 (0.4)                       | 5 (1.0)                       | 4 (0.9)  | 0                           | 11 (2.3)       |
| Palpitations   | 3 (0.6)                       | 2 (0.4)                       | 2 (0.5)  | 0                           | 7 (1.4)        |
| Congestive heart failure                             | 2 (0.4)                       | 0                             | 3 (0.7)  | 0                           | 5 (1.0)        |
| Investigations (any grade) <sup>c</sup>              | 4 (0.8)                       | 3 (0.6)                       | 3 (0.7)  | 0                           | 9 (1.9)        |

**Fig. 1 – Study design.[2]** Reprinted from The Lancet Oncology, 14, Pivot X, Gligorov J, Müller V, Barrett-Lee P, Verma S, Knoop A, Curigliano G, Semiglazov V, López-Vivanco G, Jenkins V, Scotto N, Osborne S, Fallowfield L, for the PrefHer Study Group, Preference for subcutaneous or intravenous administration of trastuzumab in patients with HER2-positive early breast cancer (PrefHer): an open-label randomised study, 962–970, Copyright (2013), with permission from Elsevier.

**Fig. 2 – Three-year event-free survival in (A) the overall evaluable ITT population, (B) the evaluable ITT population of Cohort 1, and (C) the evaluable ITT population of Cohort 2.**

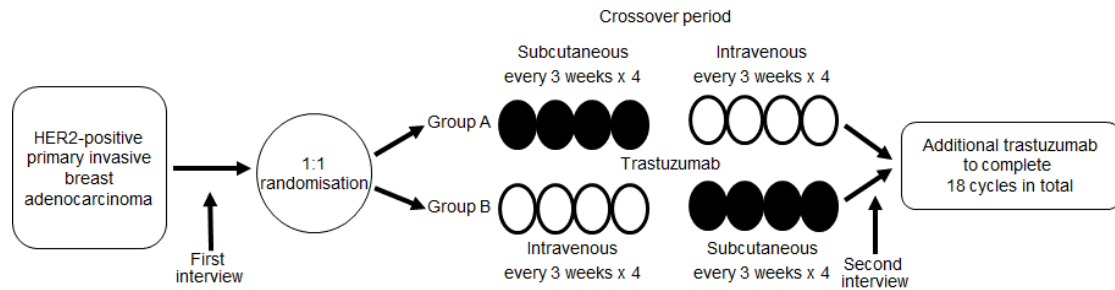
**Abbreviations:** CI, confidence interval; EFS, event-free survival; H, trastuzumab (Herceptin®); IV, intravenous; SC, subcutaneous; SID, single-use injection device.

**Appendix D: Supplementary Fig. 2 – Trial profile.** <sup>a</sup> Two patients in Cohort 1 in the H SC SID/H IV group were randomised but not treated due to non-compliance with eligibility criteria (and investigator's decision). <sup>b</sup> Two patients in Cohort 1 in the H IV/H SC SID group were randomised but not treated due to an AE and disease recurrence. <sup>c</sup> One patient in Cohort 2 in the H IV/H SC Vial group was randomised but not treated due to non-compliance with eligibility criteria.

<sup>d</sup> Three patients in Cohort 1 in the H SC SID/H IV group, who were reported to have completed treatment at the primary analysis, had in fact discontinued treatment based on investigator's decision.

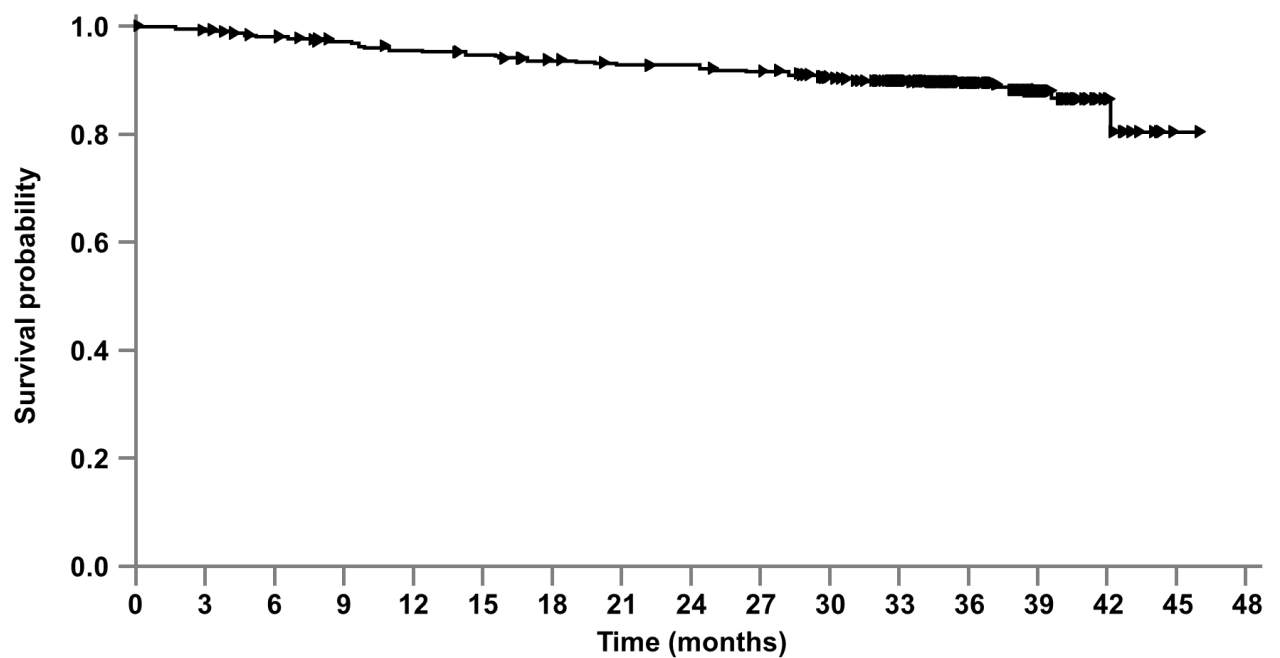
**Abbreviations:** H, trastuzumab (Herceptin®); IV, intravenous; SC, subcutaneous.

**Fig 1**

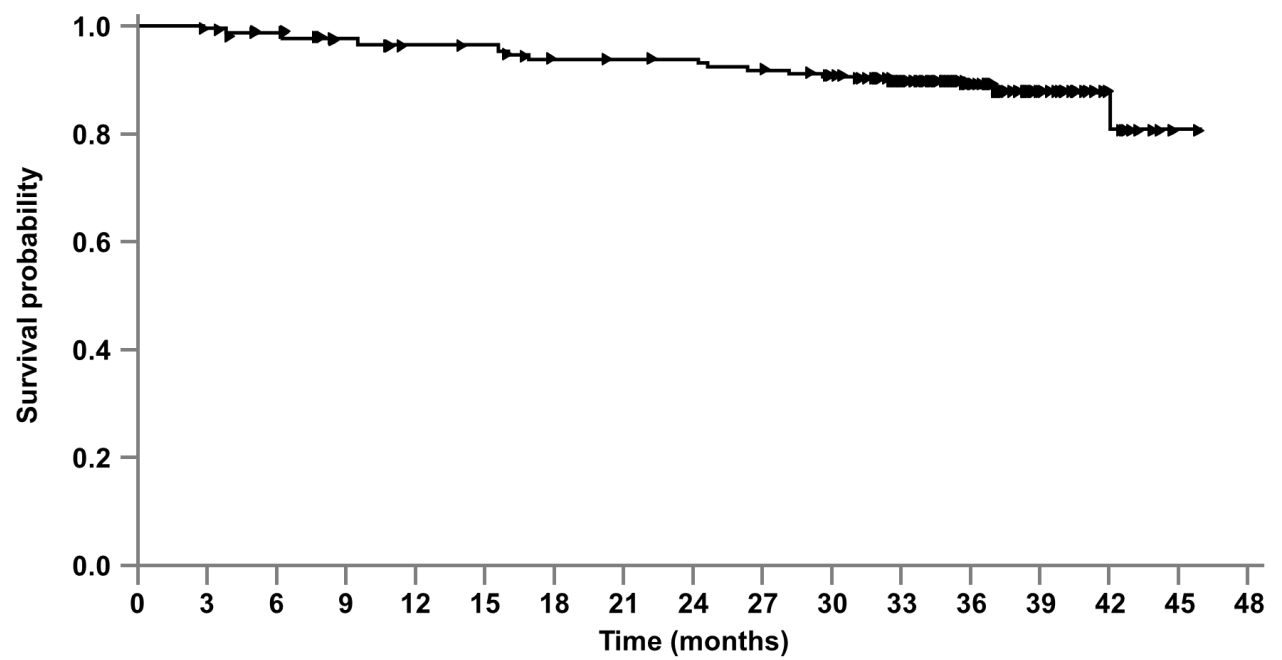


**Fig 2**

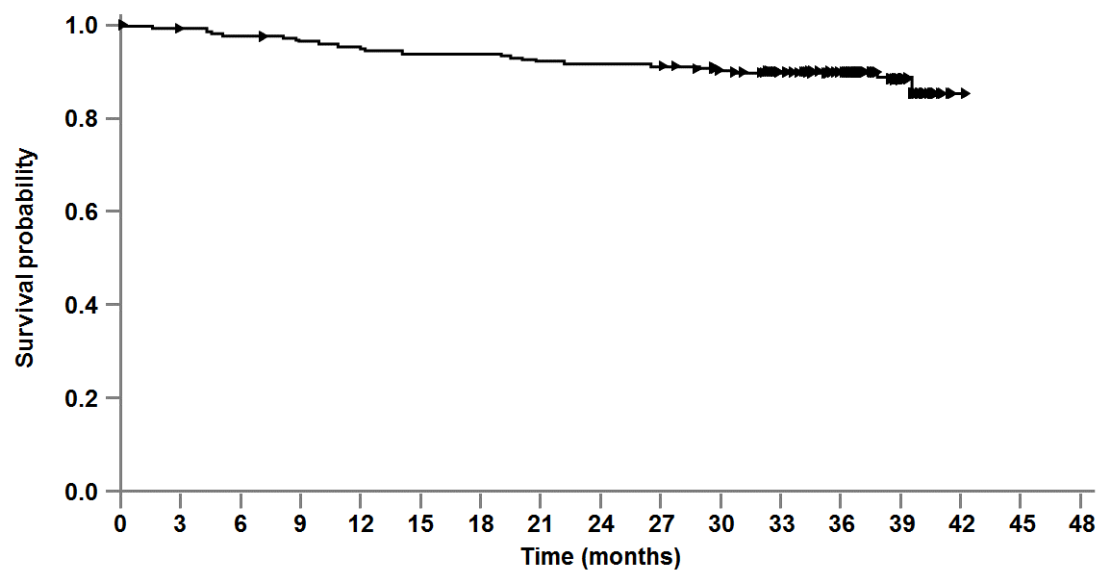
Overall (3-year EFS 90.6% [95% CI 87.4–92.9%])



**Cohort 1: H SC SID (3-year EFS 89.9% [95% CI 84.9–93.3%])**



**Cohort 2: H SC hand-held syringe from an H SC Vial (3-year EFS 91.1% [95% CI 86.6–94.2%])**



## **Appendix A: Sussex Health Outcomes Research & Education in Cancer**

### **(SHORE-C) PrefHer study team**

Lesley Fallowfield; Valerie Jenkins; Justine Kilkerr; Carolyn Langridge;

Kathryn Monson.

**Appendix B: PrefHer study investigators (Pivot X, Gligorov J, Müller V, et al. Patients' preferences for subcutaneous trastuzumab versus conventional intravenous infusion for the adjuvant treatment of HER2-positive early breast cancer: final analysis of 488 patients in the international, randomized, two-cohort PrefHer study. *Ann Oncol* 2014;25(10):1979–87).**

## **Europe**

### **Denmark**

Erik Hugger Jakobsen (Vejle Sygehus)

Mette Holck Nielsen (Odense Universitetshospital)

Soeren Linnet (Regionshospitalet Herning)

Ann Knoop (Copenhagen University Hospital)

### **France**

Xavier Pivot (University Hospital Jean Minjoz)

Herve Bonnefoi (Institut Bergonié)

Mireille Mousseau (Hôpital Albert Michallon)

Laurent Zelek (Hôpital Avicenne)

Hugues Bourgeois (Clinique Victor Hugo)

Claudia Plesse Lefeuvre (Centre Eugène Marquis)

Thomas Bachelot (Centre Léon Bérard)

Thierry Petit (Centre Paul Strauss)

Etienne Brain (Centre René Huguenin)

Christelle Levy (CRLCC-François Baclesse)

Joseph Gligorov (APHP Hôpital Tenon)

### **Germany**

Doris Augustin (Donauisar Klinikum Deggendorf)

Heiko Graf (Klinikum Meiningen Klinik für Gynäkologie und Geburtshilfe)

Georg Heinrich (Schwerpunktpraxis Dr. med. Georg Heinrich)

Hendrik Kroening (Onkologische Gemeinschaftspraxis)

Sherko Kümmel (Klinikum Essen-Mitte Ev. Huyssens-Stiftung/Knappschafts GmbH)

Volkmar Müller (University Medical Center Hamburg-Eppendorf)

Friedrich Overkamp (Praxis für Onkologie und Hämatologie)

Tjong-Won Park-Simon (Medizinische Hochschule Hannover, Klinik für Frauenheilkunde und Geburtshilfe)

Marcus Schmidt (Uniklinik Mainz)

Lidia Perlova-Griff (Sankt Gertrauden-Krankenhaus Brustzentrum)

Christopher Wolf (Dres. Christopher Wolf und Alfred Wolf)

## **Italy**

Marco Colleoni (IRCCS Istituto Europeo di Oncologia [IEO])

Alberto Ballestrero (Uni. degli Studi di Genova)

Antonio Bernardo (IRCCS Fondazione Maugeri)

Angela Stefania Ribecco (Azienda Sanitaria di Firenze—Ospedale Santa Maria Annunziata, SC Oncologia Medica)

Luca Gianni (Oncologia Medica, Ospedale San Raffaele)

Giuseppe Curigliano (European Institute of Oncology)

## **Poland**

Elżbieta Brewczynska (Maria Skłodowska Curie Memorial Cancer Centre and Institute of Oncology)

Jacek Jassem (Uniwersyteckie Centrum Kliniczne, Klinika Onkologii i Radioterapii)

## **Russia**

Vadim Shirinkin (State Institute of Healthcare Orenburg Regional Clinical Oncology Dispensary)

Alexey Manikhas (City Oncology Dispensary)

Victoria Dvornichenko (Regional Oncology Hospital)

Mikhail Lichinitser (Blokhin Cancer Research Center)

Vladimir Semiglazov (NN Petrov Research Institute of Oncology)

Guzel Mukhametshina (Republican Clinical Oncologic Dispensary of Republic of Tatarstan)

Irina Bulavina (Sverdlovsk Regional Oncology Dispensary)

## **Spain**

Enrique Espinosa Arranz (Hospital Universitario La Paz)

Francisco Carabantes Ocon (Hospital Regional Universitario Carlos Haya)

Guillermo López Vivanco (University Hospital Cruces, San Vicente de Barakaldo, Vizcaya)

Javier Salvador Bofill (Hospital Universitario Nuestra Señora de Valme)

Ignacio Porras Quintela (Hospital Universitario Reina Sofia)

Alfonso Sanchez Muñoz (Hospital Clínico Universitario Virgen de la Victoria)

Yolanda Fernández Pérez (Hospital Univ. Central de Asturias)

Javier Cassinello Espinosa (Hospital General Universitario de Guadalajara)

José Valero Alvarez (Complejo Hospitalario Zamora – Hospital Virgen de la Concha)

Rodrigo Lastra del Prado (Hospital General de San Jorge)



Luis De La Cruz Merino (Hospital Universitario Virgen Macarena)

José Manuel Pérez García (Hospital Quirón Barcelona)

Santos Enrech Frances (Hospital Universitario de Getafe)

### **Sweden**

Per Edlund (Gävle Sjukhus)

Bengt Norberg (Länssjukhuset Ryhov)

Anna-Karin Wennstig (Länssjukhuset Sundsvall)

Pehr Lind (Mälarsjukhuset)

### **Switzerland**

Nik Hauser (Kantonsspital Baden AG)

Christoph Tausch (Brustzentrum)

### **Turkey**

Celalettin Camci (Gaziantep University Medical Faculty)

Fikret Arpacı (GATA)

Huseyin Abali (Adana Baskent University Hospital)

Ruchan Uslu (Ege University Medical Faculty)

### **United Kingdom**

Saad Tahir (Broomfield Hospital)

Duncan Wheatley (Royal Cornwall Hospital)

Stephen Chan (Nottingham City Hospital)

Peter Barrett-Lee (Velindre Cancer Centre)

Karen McAdam (Peterborough District Hospital)

Richard Simcock (Brighton and Sussex University Hospital)

Russell Burcombe (Maidstone and Tunbridge Wells Hospital)

### **Canada**

Robert El-Maraghi (Royal Victoria Regional Health Centre)

Nadia Califaretti (Grand River Regional Cancer Centre)

Silvana Spadafora (Algoma Regional Cancer Program, Sault Area Hospital)

Sandeep Sehdev (William Osler Health System Brampton Civic Hospital)

Amer Sami (Saskatoon Cancer Centre, University of Saskatoon Campus)

Sunil Verma (Sunnybrook Odette Cancer Centre)

**Appendix C: Patient eligibility criteria (Pivot X, Gligorov J, Müller, V et al.**

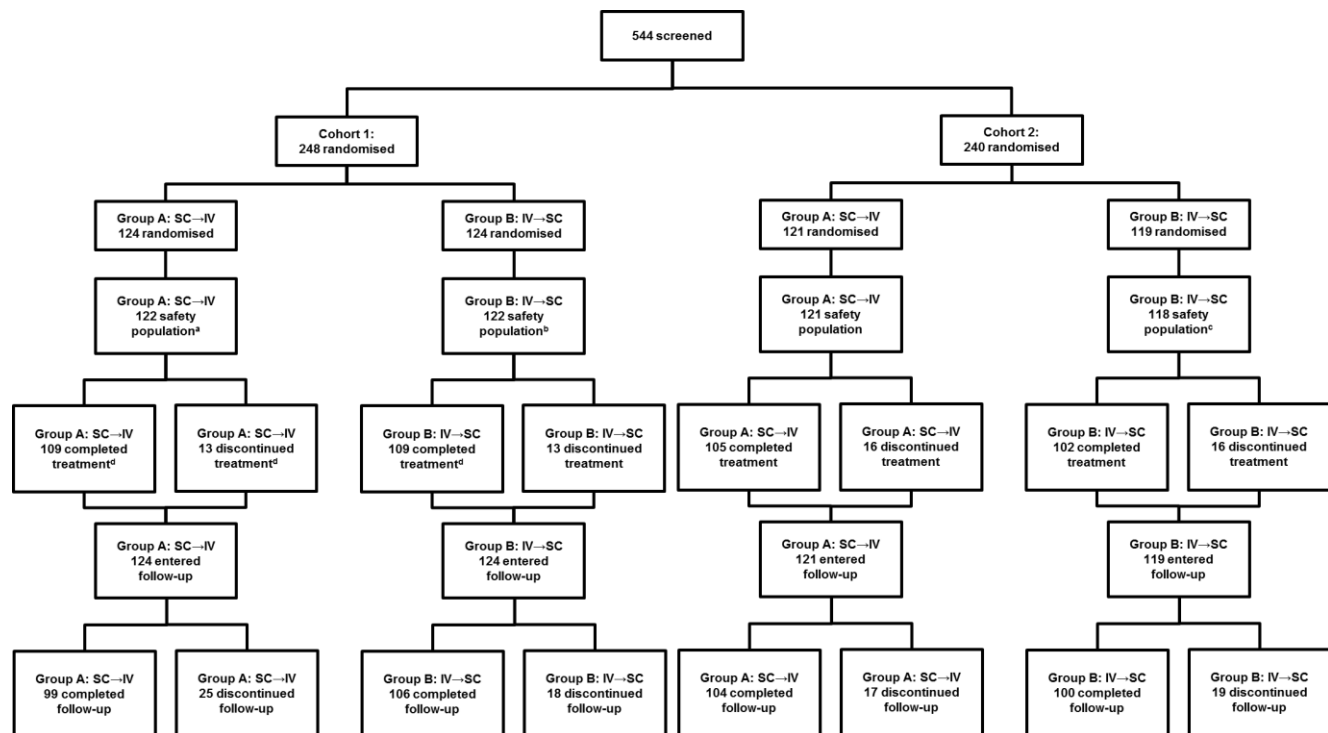
**Preference for subcutaneous or intravenous administration of trastuzumab in patients with HER2-positive early breast cancer**

**(PrefHer): an open-label randomised study. *Lancet Oncol***

**2013;14(10):962–70 and Pivot X, Gligorov J, Müller V, et al. Patients' preferences for subcutaneous trastuzumab versus conventional intravenous infusion for the adjuvant treatment of HER2-positive early breast cancer: final analysis of 488 patients in the international, randomized, two-cohort PrefHer study. *Ann Oncol* 2014;25(10):1979–87).**

Eligible patients were women aged  $\geq 18$  years with HER2-positive (immunohistochemistry 3+ or in situ hybridisation-positive), histologically confirmed primary invasive breast adenocarcinoma, no evidence of residual, locally recurrent, or metastatic disease after completion of surgery and chemotherapy (neoadjuvant or adjuvant), an Eastern Cooperative Oncology Group performance status of 0 or 1, and a baseline left ventricular ejection fraction of  $\geq 55\%$  before the first trastuzumab dose. HER2-positivity was assessed by local laboratories with validated assays, according to recommendations outlined in the summary of product characteristics for IV trastuzumab. Radiotherapy or hormone therapy was allowed. Patients had to have been either trastuzumab-naïve (*de novo* group) or already receiving intravenous trastuzumab (non-*de novo* group) as part of their (neo)adjuvant therapy, and they had to have at least eight out of the total 18 planned 3-weekly trastuzumab cycles remaining before enrolment.

## Appendix D



**Disclosures:**

SV has participated in advisory boards for Amgen, AstraZeneca, Boehringer Ingelheim, Novartis, Pfizer, and Spectrum Health, and is Medical Director and co-founder of OncologyEducation.com

VM has received speaker and consultancy honoraria from F. Hoffmann-La Roche Ltd.

ZM is an employee of, and holds stocks in, F. Hoffmann-La Roche Ltd.

SO is an employee of F. Hoffmann-La Roche Ltd.

JG has held consultancy roles for F. Hoffmann-La Roche Ltd/Genentech, Inc., and Eisai, and has received honoraria from Novartis-GlaxoSmithKline and Genomic Health.

All remaining authors have declared no conflicts of interest.

**Highlights:**

- 3-year event-free survival data in PrefHer were consistent with previous trials.
- The overall safety profile during adjuvant treatment was as expected.
- H SC was well tolerated and no new safety signals were identified.